IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 8747**
Norihito SHIMONO et al.	:	Attorney Docket No. 2002_0055A
Serial No. 10/048,063	:	Group Art Unit 1618
Filed January 28, 2002	:	Examiner Micah-Paul Young
SOLID PREPARATION CONTAINING CHITOSAN POWDER AND PROCESS FOR PRODUCING THE SAME	:	**Mail Stop: AF**

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is a Pre-Appeal Brief Request for Review.

Review is respectfully requested of the rejection of claims 29, 30, 33, 34, 37 and 38 under 35 USC 103 as being unpatentable of over the combined disclosures of Lerner et al. (US 5,840,332) in view of Dutkiewicz et al. (US 6,197,322) which is set forth in the final Official Action dated October 16, 2008.

Concurrently submitted herewith is a petition for a three month Extension of Time and a Notice of Appeal.

I. Characteristics of the present invention

(1) Claim 33 of the present invention is directed to a sustained release preparation which comprises a medicament-containing solid material as a core, and a water-insoluble coating film as a coating layer. The medicament-containing solid material consists of a medicament and a pharmaceutical excipient. The water-insoluble coating film consists essentially of a water-insoluble polymer and a chitosan powder dispersed therein. Claim 33 is further characterized by:

(i) the water-insoluble polymer is a member selected from the group consisting of ethyl cellulose, ethyl stearate-methyl methacrylate-trimethylammoniumethyl methacrylate chloride copolymer (Eudragit RS), and methyl methacrylate-ethyl acrylate copolymer (Eudragit NE30D);

(ii) the chitosan powder has a mean particle size diameter in the range of 0.5 pm to 400 μm; and

(iii) the weight ratio of said water-insoluble polymer and the chitosan powder is in the range of 1:4 to 4:1.

(2) The preparation as claimed in claim 33 exhibits superior sustained release properties in a wide range of the digestive tract.

(3) The preparation as claimed in claim 34 has further an enteric coating on the preparation of claim 33 and has sustained release properties with gastrointestinal site-specificity.

(4) The invention of claim 29 is concerned with a process for producing the preparation as claimed in claim 33, and the invention of claim 30 is concerned with a process for producing the preparation as claimed in claim 34.

II. Argument against the grounds of rejection pointed out by the Examiner

1. Firstly, the Examiner makes numerous statements in the last Office that suggests that the Examiner considers all claims to be directed to a process. See the last Office Action for example at page 2, item 3; page 4, lines 11-13; and page 6, lines 16-17. There is no word of "process" in claim 33, and such claim is clearly concerned with neither a process nor a product-by-process. Thus the Examiner gives insufficient attention to the fact that claims 33, 34, 37 and 38 are concerned with a product having the above-mentioned claimed construction.

2. With respect to the claimed ratios of chitosan and water-insoluble polymer, the Applicants have proved in numerous comparative experiments shown in Dr. Shimono's Declaration and Supplemental Declaration of record that all of the preparations of the present invention exhibit an unexpectedly superior dissolution profile (sustained release property) in comparison with all of the examples of Lerner et al. Such superior effects of the present invention could have never been predictable from Lerner et al. even by combining with Dutkiewicz et al.

With respect to these Declarations, the Examiner says in the "Response to Amendment" section on page 4 of the last Office Action that the Declaration under 37 CFR1.132 filed 7/7/08 is insufficient to overcome the rejection of claims 29, 30, 33, 34, 37 and 38 based upon USC 103(a)

because the Declaration is not commensurate in scope with the instant claims. The Examiner appears to require that all "infinite points" within the claimed range must be tested by Applicants. See the last Office Action at page 4, lines 1-3 from the bottom of the page and page 5, lines 3-4 from the bottom of the page.

The Applicants submit that the Examiner's position is wrong. The tests described in Dr. Shimono's Declaration and Supplemental Declaration cover the endpoints of the claimed range (1:4 to 4:1) and further cover various other ratios within the claimed range. The unexpected results were found in the claimed invention covering the entire claimed range. Thus, the superior sustained release effects of the preparation in the claimed range of the ratio of 1:4 to 4:1 are well supported by the experiments shown in Dr. Shimono's Declaration and Supplemental Declaration. Accordingly, Applicants submit that additional experiments are not necessary. See M.P.E.P. 716.02(d) and (e).

(i) For determining the appropriate comparative experiments, the Applicants had interviews with the Examiner on April 11, 2006 and December 18, 2006 and asked his opinion of which preparations of Lerner et al. should be compared. And, based on the interview results, the inventors made the comparative experiments faithfully following the Examiner's comments. The results of such experiments showed that the products of the present invention having the ratios within the claimed range exhibited unexpectedly superior dissolution profile (sustained release) using the 1st fluid (artificial gastric juice) and the 2nd fluid (intestinal fluid) in comparison with all of the examples of Lerner et al.

(ii) Lerner et al. discloses merely a drug release test in intestinal fluid (2nd fluid) (i.e. the data shown in Figures). See column 15, lines 47-52 of Lerner et al. One skilled in the art could never predict from the experimental results of Lerner et al. that the preparations of the present invention would exhibit such superior effects in gastric juice (1st fluid) as well as with the intestinal juice (2nd fluid), that is, unexpectedly superior sustained release effects. Such superior effects are owed to the selection of the claimed chitosan powder (selection of chitosan *per se* as a component for the coating, and using chitosan for dispersing in the water-insoluble polymer

coating, and selection of chitosan having specified particle size and the ratio to the water-insoluble polymer).

3. Against the Applicants' argument that the Lerner et al. patent does not disclose a sustained released formulation, the Examiner points outs that as indicated by the Abstract and Figures of the Lerner et al. patent, the release of the drug can be controlled by various factors including the particulate material in the coating (abstract), and further that the drug release is controlled by the varying factors including the "(4) ratio of particulate matter" (col. 11, lines 50-55) in the last Office Action, pages 5-6.

Although it is true that Lerner et al. broadly discloses that by manipulating certain parameters, any controlled release profile can be achieved, Lerner et al. tested only the drug release with intestinal fluid (2nd fluid) but no test was done with gastric juice (1st fluid). Accordingly, it could not be understood by one skilled in the art, or even assumed, from such Lerner et al. experiment whether the Lerner et al. product shows sustained release property. As mentioned above, the unexpectedly superior dissolution profile (i.e. superior sustained release property) of the present invention in comparison with the product as shown in Lerner et al. was experimentally proved by Dr. Shimono's Declaration and Supplemental Declaration with the gastric juice (1st fluid) and the intestinal fluid (2nd fluid). The Examiner has given insufficient attention to the extensive showing of unexpected results of record.

It should also be noted that the Lerner et al. patent does not mention any definition of "sustained release preparation" and shall particularly be noted that the Examiner himself has proposed for the instant claims to recite a "sustained-release" preparation to distinguish over the Lerner et al. burst type preparation at the interview with him on December 13, 2006.

4. The Examiner further pointed out that the Lerner et al. patent is silent to the specific particles size of chitosan powder, but argues that chitosan powder is a common ingredient in coating materials as is known in the art as seen in Lerner et al., and argues that the Dutkiewicz et al. patent discloses a chitosan coating suspension comprising chitosan particles ranging in size from 0.1-80 microns, and argues that it would have been well within the level of skill in the art to apply the chitosan suspension to the coating method of the Lerner et al. patent.

On this point, the Applicants have already presented detailed arguments in their response filed on July 7, 2008, particularly in Item I, (iii). However it should be emphasized that in Dutkiewicz et al., the chitosan is used in the form of a solution prepared by dissolving the chitosan homogeneously in water. Dutkiewicz et al. does not teach or suggest dispersing chitosan in a water-insoluble polymer in the specified ratio according to the claimed invention.

5. Lastly, it is respectfully submitted that the rejection is based upon an impermissible hindsight construction of the claimed invention from selected teachings of the prior art. The Examiner has failed to provide any convincing reasoning why one skilled in the art would have been motivated by the cited references to make the specific sustained release preparation of claim 33, which comprises a medicament-containing solid material as a core, and a water-insoluble coating film as a coating layer, wherein the medicament-containing solid material consists of a medicament and a pharmaceutical excipient, and the water-insoluble coating film consists essentially of a water-insoluble polymer and a chitosan powder dispersed therein, the preparation being further characterized by a specific water-insoluble polymer, a chitosan powder which has a specific mean particle size diameter in the range of 0.5 pm to 400 μm; and a specific weight ratio of the water-insoluble polymer and the chitosan powder is in the range of 1:4 to 4:1.

Thus, it is respectfully submitted that Lerner et al. and Dutkiewicz et al. does not teach or suggest the claimed invention, and that the rejection is untenable.

Favorable reconsideration and allowance is accordingly solicited.

Respectfully submitted,
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